ELEVATED BLOOD GLUCOSE RECOMMENDATION GUIDELINES THAT PRODUCE POSITIVE MATERNAL AND PERINATAL OUTCOMES AT THE UNIVERSITY OF KANSAS OBSTETRICS CLINIC

By

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Chairperson – Dr. Susan Carlson

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is a risk factor for adverse perinatal outcomes such as large for gestational age (LGA) birth, neonatal hypoglycemia and cesarean delivery.

Objective: To examine the current screening and management practices at the University of Kansas Obstetrics (KUMC OB) clinic in regard to perinatal outcomes, and adherence to recommendations from the International Association of Diabetes and Pregnancy Study Groups (IADPSG).

Design: In this retrospective analysis of 48 pregnant women with GDM, we compared IADPSG recommendations to current KUMC OB practices by investigating gestational age at screening, blood glucose levels, and perinatal outcomes.

Results: Screening within recommended timeframe occurred in 59.5%, cesarean delivery in 40.4%, neonatal hypoglycemia in 2.7%. More women who managed GDM by diet had related complications at delivery than women who were treated with medications.

Conclusion: KUMC OB produces patient outcomes that are expected when adhering to IADPSG recommendations for screening and management of GDM.

Acknowledgements

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CHAPTER I

Introduction

Gestational diabetes mellitus (GDM) is a growing problem in the U.S. and many other countries that is linked to the overall problem of overweight and obesity among adults worldwide. GDM affects an estimated 7% of all pregnancies worldwide (1). Specific numbers of this increase are difficult to determine because of a number of confounding variables; one of which is "lack of uniformity in glucose tolerance testing" (2). GDM can be nutritionally detrimental to the health of the mother as well as the infant, causing adverse outcomes such as excessive intrauterine growth (e.g., weight above the 90th percentile), cesarean delivery, neonatal hypoglycemia, and elevated cord-blood serum C-peptide (e.g., above the 90th percentile) (3). As the prevalence of GDM increases, so does the need for understanding the disease and its comorbidities. Research on this topic has increased in recent decades in an effort to reduce the prevalence of this disease and its related health issues.

The purpose of this research is to review the practices for screening, diagnosing and managing women at risk for gestational diabetes mellitus (GDM) at the University of Kansas Medical Center Obstetrics clinic (KUMC OB clinic). Careful management of blood glucose in women found to be at risk is associated with positive patient outcomes in regard to birth weight, cesarean delivery, neonatal hypoglycemia, and cord-blood serum C-peptide for GDM patients. KUMC OB clinic is currently using recommendations from the International Association of Diabetes and Pregnancy Study Groups (IADPSG) which have been inferred from result of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study that is effective in producing positive

patient outcomes such as healthy birth weight, type of delivery and cord-blood serum C-peptide below the 90th percentile.

Statement of purpose

We wanted to investigate how pregnant patients with elevated blood glucose levels at KUMC OB clinic are being managed. Specifically, we considered whether the choice of management for each patient is related to specific blood glucose thresholds; and how management compares to the IADPSG recommendations. We also examined the efficacy of management in regard to maternal and perinatal outcomes (birth weight, cesarean delivery, neonatal hypoglycemia, and cord-blood serum C-peptide).

Research questions

- The primary research question is: How are pregnant patients with elevated blood glucose levels at KUMC OB clinic managed?
    - Does choice of management relate to specific blood glucose levels?
    - How does this management compare to the IADPSG guidelines?
- A secondary question is: How effective is management in regard to maternal and perinatal outcomes (birth weight, cesarean delivery, neonatal hypoglycemia, and cord-blood serum C-peptide)?
    - How do patient outcomes compare to the HAPO study outcomes?

CHAPTER II

Literature review

Healthcare professionals have never concurred on a protocol for screening, diagnosis and management of GDM, thus there are no universally accepted detailed recommendations (4). There are general recommendations provided by many of the leading authorities on pregnancy and diabetes such as American College of Obstetricians and Gynecologists (ACOG), American Diabetes Association (ADA), and Joslin Diabetes Center. However, no one particular method has been accepted simply because "there is not enough evidence-based data proving the beneficial effect" of these methods and recommendations (5).

ACOG, ADA and Joslin are all leading authorities in GDM healthcare. ACOG is an institution that reviews new research and data regularly in the obstetric and gynecological field. The ADA is a national association that funds research and provides information and services to the public about diabetes care (6). Joslin Diabetes Center is a teaching and research affiliate of Harvard Medical School and focuses on diabetes research, clinical care and education (7).

Although there is no universally accepted recommendation for screening, diagnosis and management of GDM, the HAPO study is one of the best known and trusted studies available on the adverse outcomes for GDM. The authors of this study examined the associations between various degrees of maternal glucose intolerance and risks of adverse maternal and perinatal outcomes (5).

The HAPO study has been widely reviewed and accepted as sound evidence in the scientific community because it "was a basic epidemiological investigation that for

the first time conclusively identified strong continuous associations of maternal glucose levels below those diagnostic of diabetes with several perinatal outcomes" (8, 9). The results of this study led to the formation of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (8). The current practices at the University of Kansas Medical Center (KUMC OB) for management of women diagnosed with diabetes includes methods and recommendations inferred from the HAPO study, specifically that the tight control of blood glucose in women diagnosed with diabetes is important to reduce the adverse events noted above, and to produce positive patient outcomes such as healthy birth weight, type of delivery and cord-blood serum C-peptide below the 90th percentile. As the prevalence of GDM continues to rise, it becomes even more important to find the most beneficial and most cost-effective way to manage GDM.

Screening, diagnosis and management of GDM

A review of literature was conducted to investigate the efficacy of past and current methods used in screening, diagnosing and managing GDM. Original research studies, reviews of original research, committee opinions, and web articles were reviewed dating from 2001 to 2012. Electronic bibliographic databases used were PubMed and CINAHL. American College of Obstetricians and Gynecologists (ACOG), American Diabetes Association (ADA), Academy of Nutrition and Dietetics (AND), and Joslin Diabetes Center were also thoroughly searched. Key terms searched were gestational diabetes, management, screening, diagnosis, current practices. Several studies and leading recommendations were reviewed and examined to assess similarities and differences among them. Furthermore, the outcomes of GDM patients in these studies

were assessed to determine which similarities and differences among the methods used may result in positive maternal and perinatal outcomes.

The HAPO study was reviewed in depth because it is used by KUMC OB and because of its increasing acceptance in the obstetric community. The primary outcomes measured in the HAPO study included birth weight above the 90th percentile, primary cesarean section delivery, clinical neonatal hypoglycemia, and cord-blood serum C-peptide above the 90th percentile. Secondary outcomes measured were premature delivery, shoulder dystocia, need for intensive neonatal care, hyperbilirubinemia, and preeclampsia (9).

Risk assessment and screening

The guidelines and practices adopted by some of the leading authorities (ACOG, ADA and Joslin) vary widely. First, the risk assessment for GDM patients is recommended by all three authorities at the first prenatal visit. Low risk patients are excluded from further screening. Moderate risk patients are screened between 24–28 weeks gestation. High risk patients may be screened earlier in pregnancy, at the first prenatal visit (10).

Although these organizations are leading authorities in GDM healthcare, there is still wide variation in screening recommendations and practice. For example, in 2003, The U.S. Preventive Services Task Force declared that there is "not enough evidence to recommend screening" (10, 11). Lack of scientific-based evidence is a recurring theme in this review and is linked to the overall cost of universal screening. It applies not only to screening, but to nearly all aspects of recommendations and practices regarding GDM. It will continue to be discussed here at length.

The recommendations made by the consensus panel of the IADPSG based on the findings of the HAPO study are as follows: Risk assessment should be performed at the first prenatal visit. Low-risk patients who are of an ethnicity with low prevalence of GDM, have no family history of diabetes, are under age 25, of normal pre-pregnancy weight, and have no obstetric compromises do not necessarily need blood glucose testing (12). High-risk women should undergo testing of fasting plasma glucose, hemoglobin A1c, or random plasma glucose, based on the background frequency of abnormal glucose metabolism in the population (8).

Diagnosis

Once risk assessment and screening have taken place, the diagnosis of overt diabetes or GDM is established. However, each of the three authorities (ACOG, Joslin and ADA) recommends different diagnostic methods of screening and target blood glucose for management. ACOG recommends a screening test of 50-gram 1-hour glucose tolerance test (GTT). A result of blood glucose >130-140mg/dL, indicates need for a 100-gram 3-hour GTT to be performed. Two abnormal values from the following criteria would indicate diagnosis: Fasting≥95mg/dL, 1-hour≥180mg/dL, 2-hour≥155mg/dL, 3-hour≥140mg/dL (10, 13).

The Joslin Clinic recommends a screening test of 1-hour post-50-gram GTT>140mg/dL. 3-hour 100-gram GTT with 2 of the following abnormal values: Fasting>105mg/dL, 1-hour>190mg/dL, 2-hour>165mg/dL, 3-hour>145mg/dL (10, 14).

The ADA "guidelines state that the physician can choose one of two threshold values for the 50-g glucose load—130 mg/dL and 140-mg/dL. The values used to determine the level above which women will be tested further for diabetes differ in

sensitivity. Using a cutoff value of 130 mg/dL provides 90% sensitivity, and a 140-mg/dL cutoff value provides 80% sensitivity" (10, 15).

Studies that have evaluated these ADA diagnostic thresholds include one by Ferrara, et al. in 2007 (16). In this cohort study, the authors examined the differing thresholds recommended by the ADA and the National Diabetes Data Group (NDDG). The NDDG threshold recommendations have been used since 1979, and are not as sensitive as those of the ADA recommendations, which were published in 2000 (16).

Of the subjects in this study (16), 45,245 women met the criteria for the lower ADA thresholds, but not NDDG thresholds. These subjects' offspring were examined for macrosomia, neonatal hypoglycemia and hyperbilirubinemia. The results show that diagnosis by the more sensitive ADA criteria, yet not high enough to meet NDDG criteria for diagnosis, was associated with a decreased risk of infant macrosomia, hypoglycemia or hyperbilirubinemia (16). The lower thresholds, therefore, are recommended for use in an effort to diagnose a more appropriate number of GDM patients that should receive treatment.

Cheng, et al. (17) reach the same conclusion in their study done in 2009. These authors compared the maternal and neonatal outcomes of women without GDM to women diagnosed with GDM using the ADA recommended thresholds, referred to in this review as Carpenter-Coustan criteria, but did not meet the NDDG thresholds. The outcomes measured were cesarean delivery, operative vaginal delivery, macrosomia, and shoulder dystocia.

The authors found that women diagnosed with GDM by meeting the Carpenter-Coustan thresholds, and not high enough to meet the NDDG thresholds, had a higher

odds ratio of cesarean delivery, operative vaginal delivery, macrosomia, and shoulder dystocia. The authors recommend using the Carpenter-Coustan diagnostic thresholds, because these criteria are more sensitive than the NDDG criteria (17).

Treatment

Once GDM has been diagnosed, physicians must consider treatment regimens. Analysis of systematic reviews shows a difference in the outcomes of treatment methods of GDM. Past studies have compared treatment methods of diet, lifestyle changes, insulin use and oral hypoglycemic agents in pregnancy.

In a systematic review by Nicholson, et al. in 2009, insulin use was compared to oral hypoglycemic agents. Two trials were examined. One trial compared insulin to metformin, and the other trial compared insulin, glyburide and acarbose. The results of the trial comparing insulin and glyburide showed no significant differences in maternal glycemic control, cesarean delivery rates, or congenital malformations. The trial comparing insulin and metformin showed a higher proportion of neonatal hypoglycemia in the insulin group, with a p-value of 0.008. They concluded, however, that there was no substantial difference in maternal or neonatal outcomes between the groups (18).

A systematic review and meta-analysis by Horvath, et al. in 2010, compared diet and lifestyle changes to insulin use. The authors did not, however, compare insulin to oral hypoglycemic agents. The outcomes examined included maternal and perinatal mortality, birth injuries, mode of delivery, shoulder dystocia, preeclampsia, neonatal hypoglycemia, hyperbilirubinemia, as well as other outcomes. The results of this study showed that insulin used alone or in combination with other usual care has the most beneficial effect on these outcomes (1).

Because of the differences in evidence-based data on the treatment of GDM, there are differing recommendations by leading authorities. Three different leading authorities' recommendations were compared in an online article by The British Medical Journal in 2011. The article states that the ADA recommends that an insulin regimen be started when either fasting glucose is >105mg/dL, 1-hour postprandial glucose is >155mg/dL, or when 2-hour postprandial glucose is >130mg/dL (19). Another leading authority, the National Institute for Health and Clinical Excellence (NICE), recommends that insulin regimens should only be considered after diet and exercise have been initiated for up to two weeks and target blood glucose levels have not been met (19, 20). The Joslin Clinic recommends *against* oral hypoglycemic use (10). ACOG recommendations differ slightly, instructing that an insulin regimen should be started when either fasting glucose is >95mg/dL, 1-hour postprandial glucose is >130-140mg/dL, or when 2-hour postprandial glucose is >120mg/dL (19). ACOG also recommends that an insulin regimen only be started after diet and exercise regimens have failed to result in target glucose levels.

Outcomes of HAPO study

Catalano and associates (3) took the results of the HAPO study even further. Their subjects underwent a 75-gram OGTT between 24 and 32 weeks. GDM was diagnosed by IADPSG criteria. The authors measured for three of the four primary outcomes of the HAPO study (primary cesarean delivery, cord-blood serum C-peptide above the 90th percentile, and birth weight above the 90th percentile), and they also measured for preeclampsia. The authors divided the participants into groups: those with GDM and those with obesity because gestational diabetes mellitus and maternal obesity

have been found to be independently associated with adverse maternal and neonatal outcomes (3).

The researchers used multiple logistic regression to examine associations of GDM and obesity with the outcomes mentioned above. They found that birth weight, cord-blood serum C-peptide and primary cesarean delivery were all significantly greater in subjects with GDM compared to subjects with obesity. Preeclampsia was the only outcome measured that appeared in a greater percentage of obese women than in women with GDM. However, having a *combined* diagnosis of obesity with GDM greatly increases the likelihood of all of these primary outcomes, nearly doubling it for some outcomes (3).

Recommendations for the future

Because of the differing evidence and opinions on the screening, diagnosing and managing of GDM by all the leading authorities, the Fifth International Workshop on GDM met to review new information regarding GDM and its pathophysiology, epidemiology, perinatal outcomes, long-term mother and child implications, and management strategies, in hopes of ascertaining the most beneficial recommendations concerning GDM maternal and perinatal outcomes (2). In 2007, the panelists of the workshop published their recommendations in Diabetes Care. The panelists reviewed current research and made recommendations according the research studies.

One of the strongest recommendations made by this panel is that the translation of the HAPO study results should be of "a high priority" (2). The HAPO study is regarded highly by all leading authorities (even though ACOG says there is still lack of sound evidence as to specific diagnostic/management criteria). The panelists also state that

medical nutrition therapy (MNT) is and should be the basis of treatment for GDM. However, they go on to say that evidence-based recommendations on MNT cannot be made due to lack of substantial information (2).

ACOG is another authority that concludes more research is needed. In the 2011 Committee Opinion, ACOG states that a "universal recommendation for the ideal approach for screening and diagnosis of GDM remains elusive" (4). Evidence-based data is simply not available to make universal recommendations. The current research studies have not yet been able to demonstrate long-term data on the implications of GDM patients and their offspring. Data are still not sufficient to show which screening, diagnosing and managing techniques will be most effective in producing positive outcomes, including maternal outcomes, perinatal outcomes, long-term outcomes, and cost-effectiveness.

To date, there are no long-term randomized controlled trials that test the results of HAPO with an intervention in women. These are still needed to make evidence-based conclusions about the effects of GDM outcomes. The leading authorities on pregnancy and diabetes are many, and each has its own set of methods and practices; so finding the best way to derive positive outcomes for patients can be difficult to ascertain.

The unanimity of research on GDM and maternal and perinatal outcomes is that GDM can negatively affect the mother and child in a lasting way if not treated appropriately. There is wide consensus that GDM may lead to long term health issues for mom and baby; e.g., later development of type II diabetes (DMII), lasting effects of LGA. How to manage, treat and prevent these comorbidities is where the lack of consensus lies. Because of the lack of long-term randomized controlled-trials, evidence-

based data is not available to make universal recommendations. Further research is needed to assess precise screening techniques, diagnosing criteria and blood glucose target levels in order to derive positive outcomes for GDM patients.

CHAPTER III

Methods

The subjects of this retrospective study were pregnant women with gestational diabetes who received prenatal care at the University of Kansas Medical Center, department of Obstetrics and Gynecology (KUMC OB), and delivered at the University of Kansas Hospital. Patients were screened with the oral glucose tolerance test (OGTT) at the Johnson County Health Clinic or at the KUMC OB clinic. We included subjects who were pregnant and delivered between 2009 and 2012.

With a target of 50 subjects, we randomly selected 56 patient charts from among all women with diabetes cared for at KUMC OB clinic. Eight of these were not evaluated due to some reason including transfer of care to another facility before delivery, death of the mother or infant, or delivery of twins. The final total number of subjects included in the study was 48.

Outcome data were obtained from both paper charts and electronic medical records. Maternal characteristics recorded were age, ethnicity, pre-pregnancy weight, height, body mass index (BMI), gestational age at diabetic screening, weight at screening, year of pregnancy studied, and class of GDM (A1 versus A2). Maternal outcomes recorded were blood glucose levels at diabetic screening, daily log of blood glucose levels which were self-recorded by the women throughout pregnancy, treatments/medications and dosages throughout pregnancy, gestational age at delivery, mode of delivery (cesarean versus vaginal), and blood glucose levels at delivery and following 24 hours after delivery. Newborn outcomes recorded were birth weight, gender, blood glucose levels at delivery and following 24 hours after delivery.

IADPSG recommends screening at 24-28 weeks gestation. For glucose levels below those diagnostic of GDM, IADPSG recommends an OGTT of <92mg/dL for fasting, <180mg/dL for 1hr, and <153mg/dL for 2hr. We recorded and analyzed the OGTT fasting, 1hr and 2hr levels of mothers at screening. We also recorded and analyzed the gestational age at time of screening.

Maternal blood glucose levels were recorded daily by the patients. We recorded the number of daily glucose tests performed for each patient and divided glucose concentrations into fasting and preprandial, and determined the mean glucose level for each category. The KUMC OB clinic considers target fasting to be less than or equal to 95mg/dL, and preprandial blood glucose to be less than or equal to 110mg/dL. Any values above this, we considered 'high blood glucose.' We investigated treatment and management approaches in regard to these blood glucose concentrations.

We examined these data in two different ways. First, we compared the averages of blood glucose concentrations (women who averaged blood glucose to women who averaged blood glucose concentrations within normal limits). Second, we counted the actual number of times that the women's blood glucose concentrations were above normal limits. We then grouped the women into one of two categories: those who reported high blood glucose levels for at least 25% of their recorded tests, and those who reported high blood glucose levels for less than 25% of their recorded tests. In this way, we could examine actual number of times that blood glucose was high, instead of examining just the average.

Maternal and neonatal blood glucose levels were measured by the hospital at delivery. We also recorded blood glucose levels measured by the clinic throughout the first 24 hours after delivery. Sixteen of 48 women had repeated blood glucose testing.

Baby birth weight was measured in grams to ascertain a low birth weight, normal birth weight, or high birth weight. High birth weight is defined as a birth weight of 4000 grams or greater, and low birth weight is <2400 grams. Gestational age was dichotomized as preterm (delivered before 37 weeks) or full-term (37-42 weeks). Large for gestational age (LGA) is defined as birth weight above the 90^{th} percentile for that gestational age. We were interested in assessing neonatal cord blood serum C-peptide levels; however, this lab value was not recorded in patient charts.

Upon data completion of data collection, we compared our findings to those inferred from the HAPO study, regarding birth weight, primary cesarean delivery, neonatal hypoglycemia, and cord-blood serum C-peptide.

Ethics

This project was reviewed and approved by the Human Subjects Committee (HSC# 13520). As this retrospective chart analysis qualified for exempt status, consent was not required.

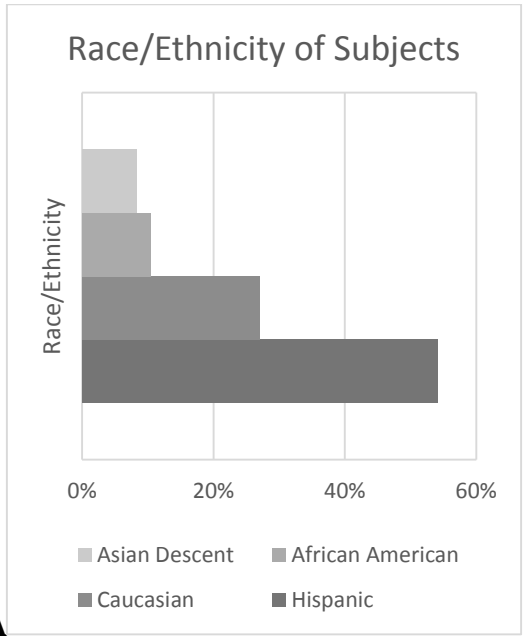
Statistical analysis

Data analysis consisted of descriptive statements. Characteristics of the study population (proportions, means and standard deviations) were determined using Excel functions. Differences found between groups and subgroups were all reported descriptively. No statistical tests were run.

CHAPTER IV

Results

Of the 48 women studied, 54.1% were Hispanic (n=26), 27% were Caucasian (n=13), 10.4% were African American (n=5), and 8.3% were of Asian descent (n=4). Age ranged from 20-45 years, and mean age was 31.4. Pre-pregnancy BMI ranged from 19.1-51.9, and mean pre-pregnancy BMI was 30.3, shown in **Figure 1**.



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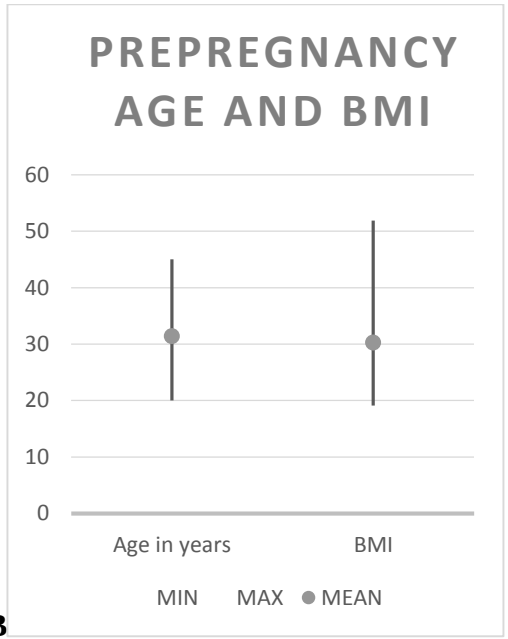

B

Figure 1. A. Demographic information on race/ethnicity of subjects. A very high proportion of the 48 subjects studied were Hispanic (54.1%) B. Range and mean of subjects' pre-pregnancy age and BMI (Body Mass Index)

A high proportion of women (78%) were overweight or obese prior to pregnancy. Thirty-six women were considered GDMA2; i.e., they controlled their blood glucose with oral hypoglycemic agents or insulin. Twelve women were GDMA1, i.e., they controlled their blood glucose with diet alone. Some women (25%) had diabetes prior to the

pregnancy studied (n=12); 6 had DMI, 5 had DMII, 1 had a history of GDM with prior pregnancies.

IADPSG recommends screening at 24-28 weeks gestation. Our subjects' gestational age at screening ranged from 5 to 32 weeks, with a mean of 25.6 weeks. Of the 48 subjects, 1 had no record of being screened at all; consequently, the following results on screening are shown for the remaining 47 subjects. The number of women screened for diabetes outside of the 24-28 week gestational age range recommended by the IADPSG was 40.4% (n=19). Of these women, 19.1% (n=9) were screened before 24 weeks gestation, and 21.2% (n=10) were screened later than 28 weeks gestation. All of the women screened before 24 weeks gestation had a pre-pregnancy diagnosis of DMI or DMII.

IADPSG recommends GDM management if the OGTT is >92 mg/dL for fasting, >180 mg/dL for 1hr, and >153 mg/dL for 2hr. The subjects in our study had an OGTT for fasting range of 68-143 mg/dL, with a mean of 91.0 mg/dL; 1hr range of 129-254 mg/dL, with a mean of 191.4 mg/dL; and a 2hr range of 109-226 mg/dL, with a mean of 164 mg/dL. Women diagnosed with overt diabetes before pregnancy were not screened with an OGTT. These women received a HgbA1c test. HgbA1c ranged from 5.2% to 9.4% among these women, with a mean of 6.39%.

Target blood glucose concentrations recommended by IADPSG are as follows: Fasting 90 mg/dL to 99 mg/dL; 1-hour postprandial <140 mg/dL; 2-hour postprandial 120 mg/dL to 127 mg/dL. Maternal blood glucose concentrations were measured and recorded daily by the patients, usually four times per day; fasting in the morning, and three at meal times. It wasn't stated in the patient charts whether glucose was checked

before or after meals; it is assumed to be preprandial. The patients with overt diabetes before pregnancy checked their blood glucose levels seven to eight times per day. For all subjects, fasting blood glucose levels ranged from 61.4 mg/dL to 108.5 mg/dL, with a mean of 80.9 mg/dL. Preprandial blood glucose levels ranged from 77.8 mg/dL to 129.6 mg/dL, with a mean of 103.7 mg/dL.

Of the women screened during the recommended timeframe of 24 to 28 weeks gestation, 57.1% averaged high blood glucose concentrations at the measurements during pregnancy and had adverse outcomes at birth, including cesarean delivery, LGA, neonatal hyperglycemia, and neonatal hypoglycemia. Of the women screened at greater than 28 weeks gestation, 50% averaged high blood glucose levels at measurements throughout pregnancy and had adverse outcomes at birth, shown in **Figure 2.**

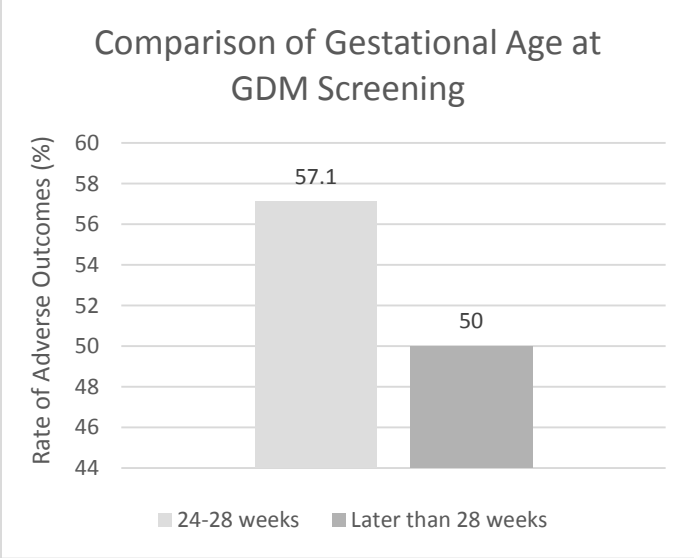

Figure 2. Comparison of rate of adverse outcomes between women who were screened for GDM between the recommended 24-28 weeks and women who were screened later than 28 weeks. Adverse outcomes include LGA, neonatal hyper- or hypoglycemia and cesarean delivery.

Women were treated with either oral hypoglycemic agents or insulin (GDMA2), or managed by diet alone (GDMA1). All of the GDMA1 women averaged blood glucose levels within normal limits throughout pregnancy; 44.7% of GDMA2 women had an

average blood glucose level that was elevated on all days recorded (mean 117.7mg/dL). A high proportion of GDMA1 women, had adverse outcomes at delivery; including 40% delivered cesarean, 20% LGA, and 30% of the newborns developed hyperglycemia. This is higher than the GDMA2 women (that also maintained high blood glucose); who had 34.2% cesarean, 7.8% LGA, 7.8% neonatal hyperglycemia, and 2.6% neonatal hypoglycemia. Total percentages of women with adverse outcomes at delivery: 60% GDMA1 and 42.1% GDMA2 (including women with both normal and high blood glucose).

The two subgroups of women (those who maintained normal blood glucose and those who maintained high blood glucose) and the rate of adverse outcomes for each subgroup is displayed in **Figure 3**.

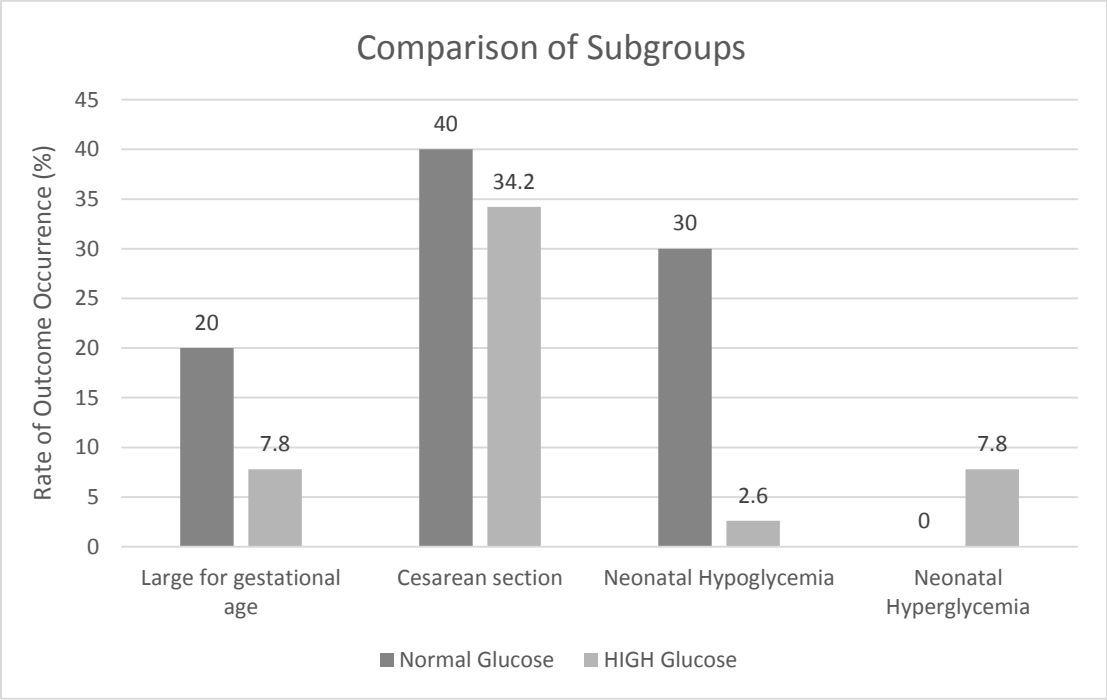

Figure 3. Comparison of outcomes of women who maintained normal blood glucose at testing throughout pregnancy to women who maintained high blood glucose at testing throughout pregnancy

The above figure is for the *averages* of blood glucose concentrations throughout pregnancy. Although this is one way to view the results, averages may not be the most accurate method to describe these results. Therefore, we examined the blood glucose concentrations in another way as well. We counted the actual number of times that the women's blood glucose concentrations were above normal limits. We then grouped the women into one of two categories: those who reported high blood glucose levels for at least 25% of their recorded tests, and those who reported high blood glucose levels for less than 25% of their recorded tests.

The results are as follows: 28 out of 48 women (58.3%) had *at least* 25% of their blood glucose test results above normal limits. 11 of these 28 women (39.2%) had adverse outcomes. Of the women who had *less than* 25% of their blood glucose test results above normal limits, 45% had adverse outcomes. Comparing these results to the previous results of the blood glucose *averages*, we find similar results, shown in **Figure 4**.

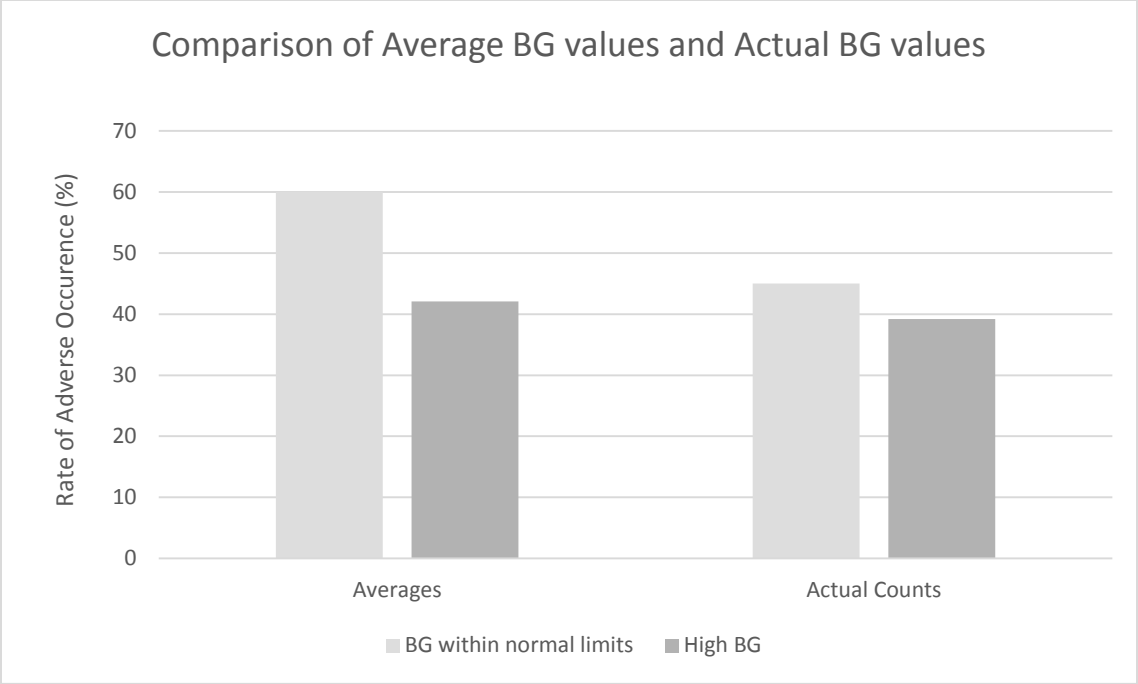

Figure 4. Comparison of rates of adverse outcomes when viewed as averages and as actual values. "*Averages*"-defined as the overall average BG level throughout pregnancy; dichotomized as averages within normal limits or averages that were high. "*Actual Counts*"-defined as the actual number of times high BG was recorded; dichotomized as less than 25% of the time (light gray column) or at least 25% of the time (dark gray column)

Due to lack of information recorded in the medical records for some of the newborns, we didn't have information on and therefore could not include 6 of the newborns. The following results pertain to only 42 newborns. Mean gestational age was 37 weeks, but a high proportion of newborns (26.1%) were born before 37 weeks gestation, and 11.9% were low birth weight and 9.5% were high birth weight.

All LGA newborns were also in the high birth weight category; these two groups are one in the same (hereon, referred to as LGA). Cesarean delivery occurred for 40.4% of the group and for 75% of LGA infants. Mean birth weight was 3073 grams. Only one newborn that was LGA was delivered vaginally, while all other LGA newborns (n=3) were delivered by cesarean section.

We also isolated the group of women who maintained an average of high blood glucose throughout pregnancy, and examined these data further. In this group, we again examined LGA, mode of delivery and neonatal hypoglycemia. This group consisted of 19 women total. Results are as follows: 10.5% were LGA, 31.5% were delivered by cesarean, and 5.2% developed neonatal hypoglycemia. We were interested in assessing neonatal cord blood serum C-peptide levels; however, this lab value was not recorded in patient charts.

We compared our results to the HAPO study results. The rates of cesarean delivery and neonatal hypoglycemia and LGA in our study were different than that of the HAPO study, shown in **Figure 5**.

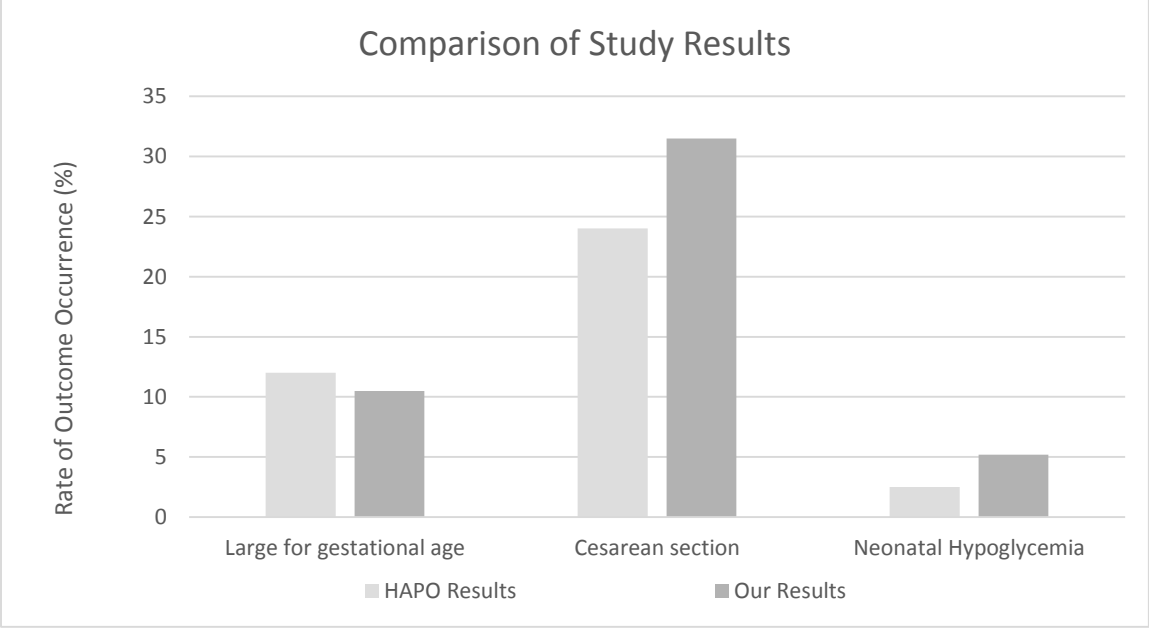

Figure 5. Occurrence of each outcome of women with high blood glucose in the HAPO compared with our study

The IADPSG recommends that all women diagnosed with GDM or overt diabetes should undergo postpartum glucose testing. In our sample, 14.5% of the women (n=7) had no record of receiving glucose testing immediately after delivery. Of the 85.5%

(n=41) of women that did receive glucose testing immediately after delivery, 61% (n=25) received only one glucose test. The other 39% (n=16) received repeated glucose tests within the 24 hour period following delivery. The range considered by University of Kansas Hospital to be within normal limits after delivery is 70-100mg/dL. Twenty-three of the 25 subjects who received only one test (92%), were within the target range of 70-100mg/dL.

Of the 41 women who received an initial glucose test at delivery, the range of initial blood glucose levels were 41 mg/dL to 17 0mg/dL, with a mean of 96.6 mg/dL. Only 16 mothers had repeated blood glucose testing. Of these women, the range of blood glucose levels were 48.2 mg/dL to 169.5 mg/dL, with a mean of 119.1 mg/dL.

Hyperglycemia occurred in 13.8% of newborns, and neonatal hypoglycemia occurred in 2.7%. Of the 42 newborns, only 36 had recorded blood glucose levels. All 36 remaining infants had repeated blood glucose testing over a 24 hour period. Blood glucose levels ranged from 48.4 mg/dL to 94.2 mg/dL, with a mean of 66.4 mg/dL. The range considered to be within normal limits is 50-80 mg/dL for neonatal glucose.

All of our results so far pertain to the total group of women studied. One confounding variable is the fact that this total group includes the women who had overt diabetes before pregnancy. In order to control for this, we removed the data of subjects with overt diabetes and examined the remaining group again. Results for the group of total subjects *without* overt diabetes are as follows: Our total number of subjects is now 37. Results for gestational age at screening and OGTT levels remains the same because the women with overt diabetes did not receive an OGTT (as stated previously, only

HgbA1c was evaluated for these women); and these women were all screened before the 24-28 week recommendation.

Other results do change when excluding the subjects with overt diabetes. Results for the GDMA1 women remain the same as reported previously because all of the subjects with overt diabetes fall into the GDMA2 category. Of the 27 GDMA2 subjects without preexisting diabetes, 51.8% had an average blood glucose level that was elevated on all days recorded. The adverse outcomes for the GDMA2 women (that also maintained high blood glucose) are as follows: 33% delivered by cesarean, 7.8% LGA, 3.7% neonatal hyperglycemia, and 2.6% neonatal hypoglycemia. The total percentage of adverse outcomes at delivery is 37%.

Again, isolating the group of women who maintained high blood glucose throughout pregnancy, but excluding the women with preexisting diabetes, our results change slightly. In this group, we again examined LGA, mode of delivery and neonatal hypoglycemia. This group consisted of 14 women total. Results are as follows: 10.5% were LGA, 28.5% were delivered by cesarean, and 5.2% developed neonatal hypoglycemia.

In other words, because there were so few subjects with preexisting diabetes, excluding these subjects from our results changes very few results. The number of subjects with preexisting diabetes was 11. Almost half of these subjects (45.5%) had adverse outcomes including cesarean delivery and neonatal hyperglycemia.

CHAPTER V

Discussion

The primary aim of this research was to ascertain how pregnant patients with elevated blood glucose levels at KUMC OB clinic are managed, in comparison to the widely accepted IADPSG recommendations.

KUMC OB management compared to IADPSG guidelines

We anticipated that differing blood glucose levels would elicit different treatments. In other words, we considered if the choice of management/treatment was related to specific glucose thresholds. Our findings did not suggest this.

Screening OGTT levels were consistent with IADPSG guidelines (<92mg/dL, <180mg/dL, <153mg/dL, for fasting, 1-hr and 2-hr, respectively). Screening gestational age was inconsistent with IADPSG, only for those screened past 28 weeks. There is no explanation as to why these women were screened late. Many of the subjects were coming from an affiliated or possibly other clinic and we did not have access to those records to know how management occurred earlier in pregnancy. However, research shows that there is no evidence to support early glucose screening.

The timeframe of 24 to 28 weeks gestation is just a recommendation by the IADPSG; there is still wide variation in screening recommendations. There is simply not enough evidence to date. Our results coincide with this idea in the sense that more of our subjects who were screened during the recommended timeframe had adverse outcomes than did the subjects who were screened *later* than the recommended time (57.1% vs. 50%, respectively). This does not suggest any benefit of earlier screening (Figure 2).

Immediate postpartum blood glucose testing was somewhat consistent with IADPSG recommendations in that some women were tested and others weren't. There was no evidence to suggest why some were tested and others weren't tested at all.

Efficacy of GDM management

The secondary aim of this research was to ascertain how GDM management relates to maternal and perinatal outcomes. We examined adverse outcomes in relation to gestational age at screening and maintenance of blood glucose levels throughout pregnancy. We then compared these findings to the HAPO study results.

As shown in the results, GDMA1 (diet only) women averaged blood glucose concentrations within normal limits throughout pregnancy but had a higher rate of adverse outcomes than did the GDMA2 (hypoglycemic agents/insulin) women, who averaged *high* blood glucose levels throughout pregnancy. We predicted that women who maintained blood glucose within normal limits would have less adverse outcomes than those with high blood glucose concentrations. Our results suggested that maintenance of blood glucose concentrations does not show positive outcomes; LGA, neonatal hypoglycemia, cesarean delivery.

One explanation for this finding may be the use of insulin and oral hypoglycemic agents. As discussed earlier, some past research has found that insulin use shows the most beneficial effects for GDM patients (1). Perhaps the use of insulin or oral hypoglycemic agents has more of an impact on perinatal outcomes than does blood glucose control.

We also investigated gestational age at screening as an indicative factor for positive outcomes. We examined outcomes at delivery as they related to gestational age

at screening. Because the IADPSG recommends screening between 24 and 28 weeks gestation, we had anticipated that those screened during that timeframe would have more positive outcomes. However, our results show that there was actually a slightly different rate of adverse outcomes for the women screened during the recommended timeframe (57.1% compared to 50% of the women screened later than recommended).

A high proportion of newborns in our study (26.1%) were born before 37 weeks gestation, which is more than double the national average for preterm birth. Worldwide preterm birth ranges between 5% and 18% (21). However, according to the Center for Disease Control, GDM patients who maintain an average high blood glucose concentration throughout pregnancy are at a higher risk for giving birth before 37 weeks gestation (22). Our results are higher than the worldwide averages; however, this is likely due to our small sample size.

Outcomes compared to HAPO findings

According to HAPO study results, at least 12% of mothers who maintained high blood glucose levels throughout pregnancy would be expected to deliver newborns that are LGA. In our sample, 10.5% of newborns were LGA. This is fairly consistent with previous findings, and perhaps our percentage is slightly different than HAPO results simply due to our small sample size (Figure 5).

We compared our results to the HAPO study results. HAPO study estimates were 23-25% of women who maintained high blood glucose throughout pregnancy would deliver by cesarean section. Our results showed 31.5% delivered by cesarean (Figure 5).

Our findings for neonatal hypoglycemia were much different than we expected. According to the HAPO study, 2.5% of newborns would be expected to develop neonatal

hypoglycemia. Our sample showed 5.2% (n=1, out of 19). Again, our sample size was very small and that may be the reason for differing results (Figure 5).

We were unable to examine cord-blood serum C-peptide because these values were not recorded in medical records.

Conclusion

To conclude, KUMC OB adheres largely to IADPSG recommendations and guidelines for GDM that have been widely accepted as the best ways to produce positive patient outcomes. However, our results indicate that there is no trend toward more positive outcomes in women who did better at maintaining blood glucose levels within normal limits compared to those who did less well; or screening between 24 and 28 weeks gestation as opposed to later. In general, all of the women had some glucose measurements above the range desired and even having fewer than one-fourth of measurements outside the desired range may not prevent adverse effects of elevated blood glucose.

Limitations

This study has several limitations. First, and foremost, the sample size is small (n=48). This may have played a role in how our findings compare to those from larger samples. Our subjects were disproportionately more Hispanic (54.1%). As expected, there seemed to be inconsistent record keeping in patient charts; certain data on some patients were missing, most likely due to random error of many different physicians entering data into the charts. More importantly, patient record keeping was unclear; specifically, there was no characterization of the timing of blood glucose in relation to meals. Blood glucose levels were irregularly recorded by the patient; some patients were

diligent in recording at every meal, while others were intermittent. Also, some of the patient record keeping was printed out by patient glucose monitor, while the others were handwritten by the patient and glucose concentrations could have been biased.

CHAPTER VI

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